REMARKS

Claims 1-6, 8, 11-21 and 23-43 are pending in the application, wherein claims 1, 8, 21, 33, 37-39 and 43 have been amended and claim 22 was cancelled. Claims 16-20 and 39-43 are currently withdrawn from consideration as being directed to non-elected inventions. However, Applicants request rejoinder of claims 16-20 and 39-43 upon the allowance of claims 1 and 20 from which they depend.

The Office Action rejects claims 1, 8, 11-13, 21-23 and 29-32 under 35 U.S.C. § 102(e) as being anticipated by Wong et al. (US 6,120,803).[1] Wong discloses a "prolonged release active agent dosage form adapted for gastric retention" that is specifically designed to persist in the stomach and release the active ingredient over a "prolonged time period", defined as meaning at least 4 hours and up to 24 hours. Col. 4, ll. 61-65; col. 28, ll. 35-36. The reason for such long retention times is to ensure proper absorption of the particular drugs (*e.g.*, acyclovir) disclosed in Wong et al. and to allow "less frequent dosing of the active agent than with immediate release formulations or sustained release formulations that are not gastric retentive dosage forms". Col. 8, ll. 20-37. This is accomplished, in part, by the use of an insoluble band of material that is wrapped around the dosage form. Col. 5, ll. 29-41. Wong et al. never address problems associated with stomach irritation caused by glucosamine or other bioactive substances and their break-down or reaction products.

Wong et al. discloses four working examples, all of which delivered the active ingredient over a period of time that exceeded about 9 hours. The formulation of Example 1 delivered 90% of the active ingredient in 8.8 hours, described as a "prolonged period of time". Col. 23, ll. 53-56. The formulation of Example 2 delivered 90% of the active ingredient in 9.6 hours. Col. 24, l. 47. The dosage form of Example 7 had a T_{90} value of approximately 9.8 hours, described as a "prolonged period of time". Col. 27, ll. 16-17. The dosage forms of Example 8 "released drug over a prolonged period and produced a T_{90} value of approximately 10.9 hours". Col. 27, ll. 49-51.

Claim 1 has been amended to define a sustained release composition that is specifically formulated to protect the stomach of a user from irritation caused by glucosamine-based or other bioactive substances that can irritate the stomach. The claimed formulation comprises powdered

[1] Applicants reserve the right to establish a date of invention that precedes the filing date of Wong et al. in order to remove Wong et al. as a reference.

cellulose and maltodextrin in which the ratio of powdered cellulose to maltodextrin is in a range of about 1:9 to about 2:3. At the upper end of the range, the amount by weight of maltodextrin is "at least about one and one-half times that of the powdered cellulose" (*i.e.*, "about 3" divided by "about 2" is about 1-1/2). Providing a mixture of powdered cellulose and maltodextrin in the claimed ratio yields an excipient that is specifically formulated "to provide a sustained release of the glucosamine-based or other bioactive substance over a period of time in a range of about one hour to about three hours and form a protective gel in order to reduce or eliminate detrimental side effects on the gastrointestinal system of the glucosamine-based or other bioactive substance, break-down products of the bioactive substance, and/or reaction products of the bioactive substance as the specimen breaks down after ingestion by a user". Support for amended claim 1 is found in the Application at paragraphs 9, 10, 18, 20 and 24 and original claim 22.

Claim 1 is not anticipated by Wong et al. because Wong et al. fails to teach or suggest an excipient composition that is able to protect the stomach from a stomach irritating bioactive substance while also providing sustained release of the bioactive substance in a range of about one hour to about three hours. The dosage form of Wong et al. is specifically designed to release the active substance for a "prolonged time period" defined as being at least 4 hours up to 24 hours. Col. 4, ll. 61-65; col. 28, ll. 35-36. Moreover, Wong et al. is entirely silent regarding protecting the stomach from irritation, thereby failing to provide a solution to this problem, particularly while releasing the bioactive substance in a time period of about one hour to about three hours rather than 4-24 hours.

Wong et al. fails to teach or suggest the selection of powdered cellulose and maltodextrin from among the many possible combinations, nor does Wong et al. provide any motivation to combine powdered cellulose and maltodextrin in the specific weight ratio of claim 1. Though Wong et al. discloses a mixture of a water soluble polymer and a hydroattractant, Wong et al. discloses 24 different water soluble polymers and 19 hydroattractants. That means there are 456 possible combinations of water soluble polymer and hydroattractant (*i.e.*, 24 times 19 equals 456). Of the 456 possible combinations, Wong et al. prefers those that contain "mixtures of polacrylic acid and polyethylene oxide or mixtures of polyacrylic acid and polyvinylpyrollidone". Col. 5, l. 65 – col. 6, l. 2. Wong et al. further discloses 41 different "non-polymeric water soluble excipients" that may be combined with the water soluble polymer

and hydroattractant, which greatly increases the number of total possible combinations to 18,696 (*i.e.*, 456 times 41 equals 18,696).

On top of the many possible combinations of components, Wong et al. discloses a wide range of possible weight ratios that go far outside the specific range defined in claim 1, which claimed range yields compositions having the specific claimed properties recited in claim 1 for protecting the stomach from irritation. According to Wong et al., the concentration of the water-soluble polymer ranges from about 5% to about 90% by weight of the matrix, and the concentration of the hydroattractant ranges from about 5% to about 70%. That means that the hydroattractant can have a concentration that is up to 14 times the concentration of the water soluble polymer (*i.e.*, 70% divided by 5% equals 14). That is 21 times more than the upper limit of the weight ratio of powdered cellulose to maltodextrin (*i.e.*, 2:3) within claim 1. There are literally millions of different compositions disclosed within Wong et al., only a small percentage of which can even arguably fall within the scope of claim 1.

According to the Federal Circuit, a claim that defines a well-tailored species of compositions having specific properties or characteristics not taught or understood in the cited art is patentable over a reference that discloses a broad genus covering compositions that both posses and lack the claimed properties or characteristics, particularly if the claimed composition is different from the stated preferences disclosed in the cited reference. *Ultradent Products, Inc. v. Life-Like Cosmetics*, 127 F.3d 1065, 1071 (Fed. Cir. 1997). In *Ultradent*, the Federal Circuit specifically found that a patent that disclosed a concentration range of 0.05% to 5% for a particular component known to increase viscosity resulted in at least "millions" of potential combinations. *Id.* at 1072. However, the specific examples in the reference all fell outside the claims, which claimed a specific type of stickiness, and the Court upheld a jury verdict that found that the reference failed to describe any compositions within the claims at issue. *Id.* at 1070. In making its ruling, the Federal Circuit relied on *In re Petering*, 301 F.2d 676, 681 (CCPA 1962), which held that unless the preferences within a generic disclosure narrow the possible combinations to a small number, the disclosure of a genus does not disclose a species within the genus.

The CCPA further ruled in *In re Ruschig*, 343 F.2d 965, 974 (CCPA 1965) that unless a cited reference discloses a small recognizable class with common properties, the disclosure of a broad genus does not disclose a species within that genus. In *Ruschig*, the cited art included a

generic disclosure which yielded 130 and 259 possible compounds, but no specific species of compounds like those in the claims at issue.

The teachings of *Ultradent*, *Petering* and *Ruschig* is clear. If the cited reference does not expressly and specifically disclose an anticipating composition, a court (or PTO) must determine whether the reference teaches an invalidating species "from among the many possible candidates". To engage in this analysis, the court or PTO should first look to the number of combinations that could be prepared using the disclosure of the cited reference. If that number is large, the court or PTO should look to the preferences to see what extent the number of possible combinations is reduced. If the resulting number is large, *e.g.*, 130 or more as in *Ruschig*, the reference does not invalidate. If the resulting number is small, *e.g.*, 20 or less, as in *Petering*, the court or PTO must then determine whether any of the 20 or so combinations satisfies the claim limitations. If not, the reference does not invalidate.

In the present case, Wong et al. discloses 456 possible combinations of water soluble polymer and hydroattractant, only one of which satisfies claim 1. None of the examples include maltodextrin, let alone a combination of maltodextrin and powdered cellulose. Moreover, Wong et al. discloses a very broad range of possible weight ratios of hydroattractant to water soluble polymer, the upper end of which exceeds the upper limit of claim 1 by 21 times. According to *Ultradent*, Wong et al. discloses "millions" of possible compositions when the concentration range is taken into account, only a minor portion of which fall within the scope of claim 1. According to *Ruschig*, Wong et al. discloses a "large" number of possible combinations within the broadly disclosed genus, but does not describe the species of claim 1. Moreover, none of the examples of Wong et al. fall within the scope of claim 1, and Wong et al. fails to disclose a narrow range of compositions (*e.g.*, 20 as in *Petering*) that have the common property recited in claim 1 (*i.e.*, of protecting the stomach while permitting release of the bioactive substance in a time period of about one to about three hours). Wong et al. therefore utterly fails to teach or suggest the specific composition of claim 1 (*i.e.*, that (i) has the specific selection of powdered cellulose and maltodextrin from among 456 possible combinations, (ii) within the claimed weight ratio from among "millions" of possible weight ratios, (iii) to yield a composition having the claimed properties of releasing the bioactive substance within about one to three hours while forming a gel to protect the gastrointestinal system from irritation by the bioactive substance, breakdown product, and/or reaction product).

Because claim 1 is patentable over Wong et al., Applicants submit that dependent claims 2-6, 8, and 11-20 are likewise patentable over Wong et al. for at least the reasons given above.

Claim 21 alternatively claims a sustained release orally administered specimen that includes "a sustained release composition" and "a bioactive substance mixed with the sustained release composition throughout the orally administered specimen". The sustained release composition comprises powdered cellulose and maltodextrin in an amount such that "the amount of maltodextrin exceeds the amount of powdered cellulose". Application, ¶ 24. The "sustained release composition forms a protective gel to prevent direct contact between at least a portion of the bioactive substance and a stomach wall and reduce or eliminate detrimental side effects on the gastrointestinal system of the bioactive substance, break-down products of the bioactive substance, and/or reaction products of the bioactive substance as the specimen breaks down". As discussed above, Wong et al. utterly fails to teach or suggest (i) selecting powdered cellulose and maltodextrin from among 456 different possible combinations, (ii) within the claimed weight ratio from among "millions" of possible weight ratios, (iii) to yield a composition having the claimed properties of releasing the bioactive substance within about one to three hours while forming a gel to protect the gastrointestinal system from irritation by the bioactive substance, breakdown product, and/or reaction product. Accordingly, Applicants submit that claim 21 as amended is neither anticipated by nor obvious over Wong et al., either alone or in combination with any other art of record. Dependent claims 23-32 and 39-43 are likewise believed to be patentable.

The Office Action rejects claims 1, 8, 11, 21, 29 and 32 under 35 U.S.C. § 103(a) as being unpatentable over Bertini et al. (US 6,096,172). Bertini et al. discloses (R)-2-(3-benzoylphenyl,) propionic acid salts and a wide variety of pharmaceutical preparations containing them, including oral, injectable, topical, sublingual, aerosol nasal spray, and mouth wash. Col. 1, ll. 5-8; col. 10, ll. 15-32. Bertini et al. discloses formulations that may include 10-80% of "excipients such as lactose, microcrystalline cellulose, powdered cellulose, starch and various maltodextrins, calcium hydrogenphosphate, silica and the mixture in the presence of binding substances (at a concentration of from 2 to 10%), such as polyvinylpyrrolidone, alginates, carboxymethylcellulose sodium, carboxymethylcellulose starch". Col. 10, ll. 39-46. There are literally dozens of possible combinations of the foregoing in no specified weight ratio. Thus, the discussion above relative to Wong in light of the rules articulated in *Ultradent,*

Petering, and Ruschig, are also applicable to Bertini et al. Though the PTO argues that Bertini et al. disclose a genus that includes the species of claims 1 and 21, Bertini et al. utterly fails to teach or suggest (i) selecting powdered cellulose and maltodextrin from among the dozens of possible combinations, (ii) within the claimed weight ratio from among "millions" of possible weight ratios, since none is specified, (iii) to yield a composition having the claimed properties of releasing the bioactive substance within about one to three hours while forming a gel to protect the gastrointestinal system from irritation by the bioactive substance, breakdown product, and/or reaction product. In fact, the Office Action concedes that "Bertini does not teach the sustained release time period". For this reason, claim 22 was not rejected over Bertini by itself. Because claims 1 and 21 have been amended to recite the sustained release time period of claim 22, Applicants submit that claims 1 and 21 are further patentable over Bertini for this additional reason.

Because Bertini et al. admittedly fails to "teach the sustained release time period", the Office Action attempts to combine Bertini et al. with Baichwal et al. (US 5,128,143) when rejecting dependent claims 22 and 23. The Office Action alleges that Baichwal et al. teaches that "[t]he dissolution time for the active medication is within about 3.5-5 hours". This is an incorrect reading of Baichwal et al., which actually teaches that "50 percent of the medicament will dissolve in distilled water within about 3.5-5 hours". Col. 9, ll. 45-48 (emphasis added). Baichwal et al. is entirely silent with respect to how fast the medicament would be released within the stomach. Moreover, "50 percent" is only half of the medicament, which means the overall sustained release time period is significantly longer than "about 3.5-5 hours". Finally, the combined teachings of Bertini et al. and Baichwal et al. fail to teach or suggest (i) selecting powdered cellulose and maltodextrin from among the dozens of possible combinations, (ii) within the claimed weight ratio from among "millions" of possible weight ratios, since none is specified, (iii) to yield a composition having the claimed properties of releasing the bioactive substance within about one to three hours while forming a gel to protect the gastrointestinal system from irritation by the bioactive substance, breakdown product, and/or reaction product. The same would be true for any alleged combination of Wong et al. and Baichwal et al. Accordingly, Applicants submit that claims 1 and 21 as amended are unobvious over the combination of Bertini et al. and Baichwal et al. or any alleged combination of Wong et al. and Baichwal et al.

The Office Action rejects claims 2-6, 33 and 35-38 under 35 U.S.C. § 103(a) as being unpatentable over Bertini et al. and Lord et al. (US 6,417,227). The Office Action admits that Bertini is "silent as to the teaching of the specific medicament being claimed". For this reason, the Office Action attempts to combine Bertini et al. with Lord et al. Like Bertini et al., Lord et al. also discloses a variety of different dosage forms, including "transdermal delivery devices, suppositories, enterically coated compositions, and microencapsulated compositions". Col. 1, ll. 50-53. With respect to oral medicaments, Lord et al. specifically provides for coatings that prevent dissolution of the drug in the stomach in order for the drug to reach the small intestine. Col. 7, l. 55 – col. 8, l. 19. "Enteric coatings are used to deliver drugs to the small intestine and to protect drugs from inactivation by gastric enzymes or low pH." Col. 7, ll. 55-57. "The coatings provide an impermeable barrier which will not readily dissolve or disperse at the low pH of the gastric juices of the stomach. However, at the higher pH of the intestinal fluids the enteric coating will dissolve or disperse allowing for absorption of the drug." Col. 7, ll. 63-67 (emphasis added). Thus, Lord et al. is clear that the enterically coated oral drug must be formulated to avoid being absorbed in the stomach so as to persist until it reaches the intestine. Lord et al. teaches the exact same thing relative to microencapsulation: "CM can also be coated by microencapsulation to provide for release in the small intestine instead of the stomach." Col. 8, ll. 41-42 (emphasis added).

In contrast to Bertini et al., which neither teaches nor suggests the medicament recited in claim 33, or Lord et al., which specifies that the oral dosage form must be formulated in order to pass unaffected through the stomach into the intestine, claim 33 recites "a sustained release orally administered specimen" that "breaks down in the stomach". *See* Application, ¶ 20 (protective gel formed by powdered cellulose and maltodextrin in the claimed ratio acts as a "stomach guard" to protect the "stomach lining" as the medicament is released). Because Bertini et al. admittedly fails to "teach the sustained release time period" and because Lord et al. specifies an oral dosage form that is formulated to pass largely unaffected through the stomach and into the intestine, the combined teachings of Bertini et al. and Lord et al. fail to teach or suggest a dosage form that specifically "breaks down in the stomach". More fundamentally, the combined teachings of Bertini et al. and Lord et al. fail to teach or suggest (i) selecting powdered cellulose and maltodextrin from among the many possible combinations, (ii) within the claimed weight ratio from among "millions" of possible weight ratios, since none is specified, (iii) to

yield a composition having the claimed properties of releasing the bioactive substance within the stomach while forming a gel to "act as a stomach guard" as the specimen breaks down.

The Office Action rejects claims 1-6, 8, 11-13, 21-33 and 35-38 under 35 U.S.C. § 103(a) as being unpatentable over Wong et al. in view of Lord et al. As discussed above relative to claim 1, Wong et al. fails to teach or suggest a dosage form that, among other things, provides sustained release of a "bioactive substance over a period of time in a range of about one hour to about three hours". Instead, Wong et al. discloses a delivery device that takes "at least 4 hours" and up to 24 hours to break down. Moreover, one of skill in the art would not have been motivated to combine Wong et al. and Lord et al. On the one hand, Wong et al. expressly teaches a device that is specifically designed to remain in the stomach while it breaks down so as to not pass into the intestine: "The invention provides for initial and substantially complete delivery of an active agent formulation in the stomach of a user". Col. 8, ll. 23-25 (emphasis added). In direct opposition to Wong et al., Lord et al. discloses a microencapsulated drug in tablet form that will "provide for release in the small intestine instead of the stomach". Col. 8, ll. 41-42 (emphasis added). Thus, the teachings of Wong et al. and Lord et al. are completely at odds with each other. More fundamentally, even if combined, the combined teachings of Wong et al. and Lord et al. fail to teach or suggest (i) selecting powdered cellulose and maltodextrin from among 456 possible combinations, (ii) within the claimed weight ratio from among "millions" of possible weight ratios, (iii) to yield a composition having the claimed properties of releasing the bioactive substance within about one to three hours while forming a gel to protect the gastrointestinal system from irritation by the bioactive substance, breakdown product, and/or reaction product. For this reason, Applicants submit that independent claims 1 and 21, as well as the claims which depend therefrom, are unobvious over Wong et al. and Lord et al.

With respect to claim 33, the Office Action admits that Wong et al. "is silent with respect to the specific active agents being claimed". For this reason, Wong et al. was combined with Lord et al. However, as discussed above, Lord et al. expressly teaches a dosage form for delivering the disclosed medicaments "in the small intestine instead of the stomach". Col. 8, ll. 41-42. For this reason, one of skill in the art would not have been motivated to use the medicaments of Lord et al., which are specifically intended to be absorbed "in the small intestine instead of the stomach", with the delivery device of Wong et al., which is specifically designed to remain the in the stomach for up to 24 hours. More fundamentally, the combined teachings of

Wong et al. and Lord et al. fail to teach or suggest (i) selecting powdered cellulose and maltodextrin from among the 456 possible combinations in Wong et al., (ii) within the claimed weight ratio from among "millions" of possible weight ratios, (iii) to yield a composition having the claimed properties of releasing the bioactive substance within the stomach while forming a gel to "act as a stomach guard" as the specimen breaks down.

With respect to the claimed weight ratio of powdered cellulose and maltodextrin, it is indeed "critical" to the invention because it yields a sustained release composition having the specific gelling and gastrointestinal protection properties recited in the claims. As such, the claimed weight ratios are a "result-effective variable" that is neither understood nor taught in any of the cited references. According to the MPEP, "[a] particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." MPEP § 2144.05 (II)(B) (citing *In re Antonie*, 559 F.2d 618 (CCPA 1977)). In the present case, none of the cited references teach or suggest selecting any particular weight ratio of powdered cellulose and maltodextrin in order to form a gel in the stomach that acts as a stomach guard to protect the stomach wall from the effects of an irritating bioactive substance. Because the cited references are all silent with respect to protecting the stomach, they provide no recognition of the result-effective variable claimed in the present application (*i.e.*, a ratio of powdered cellulose and maltodextrin to yield a composition that can form a gel to protect the stomach from being irritated by the bioactive agent). As a result, the PTO's reliance on *In re Aller* is misplaced according to MPEP § 2144.05 (II)(B).

Finally, the statement in the Office Action that "Baichwal or Lord is relied upon solely for the teaching of the release time or the active agent" (emphasis added) is contrary to accepted examining procedures. According to the MPEP, the PTO may not pick and choose from a reference only so much as will support an examiner's rejection, while ignoring contrary teachings that lead away from the claimed invention. MPEP § 2141.02 ("A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)"). For example, Lord et al. contains teachings that are so contrary to Wong et al. as to lead away from the alleged motivation to

combine to obtain the claimed invention, as discussed above. Thus, Lord et al. may not be "relied upon solely for the teaching of ... the active agent" as alleged in the Office Action.

In view of the foregoing, Applicants submit that the claims as now amended are in allowable form. In the event that the Examiner finds any remaining impediment to a prompt allowance of this application that may be clarified through a telephone interview, or that may be overcome by an Examiner's Amendment, the Examiner is requested to contact the undersigned attorney.

Dated this 18th day of October 2005.

Respectfully submitted,

JOHN M. GUYNN
Attorney for Applicants
Registration No. 36,153
Customer No. 022913

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